CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22404Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY TL NDA REVIEW AND EVALUATION

Application number:	22-404
Supporting document/s:	IND 69,578, NDA 18-040, NDA 18-888
Applicant's letter date:	June 15, 2009 (resubmission after RTF)
CDER stamp date:	June 16, 2009
Product:	ORAVIG (miconazole) buccal tablets, 50 mg
Drug class/Indication:	Imidazole antifungal for the local treatment of oropharangeal candidiasis
Applicant:	BioAlliance Pharma, c/o Beckloff Associates, Overland Park, KS
Review Division:	Division of Special Pathogen and Transplant Products
Reviewer:	William H. Taylor, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Judit Milstein
Date Review Completed	April 14, 2010

Pharmacology/Toxicology Team Leader Review

Background

Miconazole is an imidazole antifungal that was originally approved in 1974, and may be currently marketed under active NDAs and ANDAs for drug substance formulations, including emulsion, cream, ointment, lotion, and vaginal suppository formulations. (b) (4) . Other formulations, including aerosol powders, shampoos, solutions, controlled release patches, tablets, tampons, and injectables have been studied, and products have been submitted under INDs, NDAs, or ANDAs that are currently cancelled, withdrawn, discontinued, inactivated, or terminated. Currently marketed miconazole products include OTC products.

BioAlliance Pharma submitted Pre-IND 69,578 and met with DSPTP during 2004, to discuss a 505(b)(2) application for a new (b) (4) (b) (4) buccal tablet for treatment of oropharyngeal candidiasis. BioAlliance Pharma submitted an Original IND in 2005. On February 5, 2009, the company initially submitted NDA 22-404, under 505(b)(2) of the FD&C Act, for (b) (4) buccal tablet for the local treatment of oropharyngeal candidiasis. Following a refuse-to-file for manufacturing reasons (product tablets were lacking a required code imprint), the applicant resubmitted the application on June 15, 2009. On August 26, 2009, the filing was accepted and communicated with the applicant.

The Pharmacology/Toxicology portion of the application consists of (1) three original animal studies; (2) labeling from Monistat i.v. (NDA 18-040), Monistat 3 (NDA 18-888), and Monistat Dual-Pak (NDA 20-968) products; (3) reprints of three journal articles; (4) a reprint of labeling information published in a 1990 Physicians' Desk Reference; and (5) a reprint of a redacted Pharmacology/Toxicology Review for NDA 20-968 (Monistat Dual-Pak).

The original animal study reports were submitted to address DSPTP safety concerns for local toxicity; the remaining materials were submitted to support labeling for Sections 8.1 (Pregnancy), 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), and 13.2 (Animal Toxicology and/or Pharmacology).

The animal studies consisted of two hamster studies and a mouse local lymph node assay (LLNA) to assess local toxicity.

In the hamster studies, a paste of miconazole nitrate (1000 mg/kg) was placed into the buccal area (pouch) of animals. The intent was to evaluate the animals over two weeks. But in the first study, serious adverse clinical signs were noted by Day 4 (including hypoactivity and reduced food and water consumption), and 5/10 treated animals died on Days 5 and 6. The study was terminated on Day 6. Animal deaths were attributed to swallowing the paste and possible systemic exposure to levels of miconazole exceeding LD_{50} values. A repeat study in hamsters was begun in which a mouth rinse was planned at 4 hours, but this study, too, resulted in early animal deaths and was terminated. Histopathologic examination of animal cheek pouches revealed thickness of the epithelium, inflammation, and dilated blood vessels.

The LLNA was conducted in mice per standard protocol, and the result was that miconazole did not produce local irritation.

The applicant's materials submitted to support labeling were discussed extensively with FDA General Counsel, primarily through the DSPTP Supervisory Regulatory Project Manager, Ms. Judit Milstein, and the Office of Antimicrobial Products Associate Director for Regulatory Affairs, Mr. David L. Roeder. GC disallowed the Physicians' Desk Reference under 505(b)(2) to support labeling for NDA 22-404 because the information is not an original source or peer reviewed. GC also disallowed the submitted labeling

and the redacted Pharm/Tox review of NDA 20-968, because NDA 20-968 was delisted from the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Consequently, some of the language recommended for Sections 8.1, 13.1 and 13.2 of the label was obtained by the DSPTP Pharm/Tox team from additional published literature. For more information, please refer to the primary Pharmacology/Toxicology review by Owen G. McMaster, Ph.D.

Analysis, Conclusions and Recommendations

The hamster studies submitted by the applicant to NDA 22-404 produced severe toxicity, including death. However, the deaths were probably a secondary effect of systemic drug exposure and/or lack of eating. Inflammation observed histopathologically in the cheek tissue was probably drug-related, but since the concentration of drug substance was probably too high, and multiple concentrations were not tested, the significance of the findings to the clinical situation is unknown (i.e., the results are uninterpretable). The LLNA results (no local irritation) are at odds with the in vivo hamster findings.

Clinical trials showed the buccal application of miconazole produces minimal systemic exposure, and measures of local irritation in patients were not significantly different from those from the comparator product (clotrimazole troches) or miconazole gel (marketed in Europe). (Refer to the Clinical Reviewer review and the most recent product label for details.)

I conclude that, because miconazole has been marketed for more than 30 years, and most of the clinical experience has been with topical formulations (especially intravaginal applications), the clinical experience is sufficient to assess safety of the Oravig product at this time, without further consideration of, or need for additional nonclinical data.

I conclude the published literature submitted by the applicant to support labeling, which was allowed by FDA General Council, supports product labeling.

I agree with Dr. McMaster's conclusion to recommend approval of this application. I also agree with his conclusion that further nonclinical studies are not needed. Finally, I agree with the labeling recommendations presented in Dr. McMaster's review.

William H. Taylor, PhD, DABT
Pharmacology/Toxicology Supervisor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	ORAVIG (miconazole) buccal tablets

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/s/

WILLIAM H Taylor
04/15/2010

RENATA ALBRECHT
04/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

NDA NUMBER:	**22-404**
SERIAL NUMBER:	**9**
DATE RECEIVED BY CENTER:	**06/16/2009**
PRODUCT:	**ORAVIG**
INTENDED CLINICAL POPULATION:	**Patients with oropharyngeal candidiasis**
APPLICANT:	**BioAlliance Pharma**
	c/o Beckloff Associates
	7400 West 110th St, Suite 300
	Overland Park, Kansas 66210
DOCUMENTS REVIEWED:	**Nonclinical studies**
REVIEW DIVISION:	**Division of Special Pathogens and Transplant**
	Drug Products (HFD-590)
PHARM/TOX REVIEWER:	**Owen McMaster, Ph.D.**
PHARM/TOX SUPERVISOR:	**William Taylor, Ph.D.**
DIVISION DIRECTOR:	**Renata Albrecht, M.D.**
PROJECT MANAGER:	**Judit Milstein**

DATE OF REVIEW SUBMISSION TO DARRTS: **April 14, 2010**

1. EXECUTIVE SUMMARY

1.1 Recommendations

1.1.1 Approvability

There are no nonclinical pharmacology or toxicology data that preclude the approval of ORAVIG.

Nonclinical studies

No additional nonclinical studies are being recommended at this time.

1.1.3 Labeling

Please see the 'Recommended labeling' section at the end of this review.

1.2. Brief discussion of nonclinical findings

A. Brief overview of nonclinical findings

ORAVIG buccal tablets are indicated for use in patients with oropharyngeal candidiasis and are to be applied to the upper gum region (canine fossa) once daily for 14 consecutive days. Each tablet contains 50 mg of miconazole, a drug which has been approved in many countries for over three decades. An oral miconazole formulation, Daktarin® oral gel, is available outside of the US. The dose of miconazole in the approved oral gel is around 250 mg/day but clinical trials in North African patients have studied doses of 500 mg/day for 14 days. Given extensive clinical experience with higher oral doses of miconazole, the proposed dose of miconazole in ORAVIG, 50 mg/day, appears to be safe. As a part of this 505(b) (2) submission, BioAlliance Pharma therefore conducted a limited bridging toxicology program with ORAVIG to evaluate the potential of this new formulation to cause irritation and to induce delayed contact hypersensitivity. The sponsor submitted three nonclinical toxicology studies, and the results of literature searches related to miconazole, milk protein concentrate and mucoadhesive delivery of pharmaceuticals.

The irritating potential of ORAVIG was evaluated in two nonclinical studies by finely crushing the buccal tablet and preparing a paste with 0.9 % saline, which was then administered into the cheek pouch of gold hamsters (*Mesocricetus auratus)*. Hamsters rejected material from the cheek pouch, and poor clinical condition/mortality on Day 5 precluded continued exposure of the oral mucosa beyond Day 5. The adverse effects were likely due to rejection and swallowing of test material and systemic exposure to the drug, as the dose (1000 mg/kg/day) was above the acute LD_{50} values known for other species (160-276 mg/kg). This rejection of test material has been reported in other studies and some researchers have even resorted to suturing the cheek pouch to keep the test materials in place.

No additional nonclinical studies are being recommended at this time. Although nonclinical studies were requested by the agency, the applicant has twice attempted to evaluate the irritating potential of ORAVIG in hamsters without success. While the "pouch-in-pouch" technique may increase retention of the test material, this could require repeated suturing of the hamster cheek pouch, which could confound interpretation of any findings.

Nonetheless, based on the limited nonclinical data obtained in the hamster cheek pouch studies, the irritant effects of ORAVIG appear to be mild. After 5 days, the jugal mucosa of surviving animals revealed orthokeratotic hyperkeratosis which was sometimes associated with minimal inflammation and dilated blood vessels. This effect was likely the consequence of lack of keratin shedding. The local adverse events reported in clinical trials of ORAVIG were similar to local adverse events reported for miconazole gel and for clotrimazole troche (see Clinical Review by Medical Officer Dr. Hala Shamsuddin). ORAVIG did not induce contact hypersensitivity in mice in the local lymph node assay. ORAVIG did not cause significant lymphoproliferation or local irritation at concentrations up to 5 %.

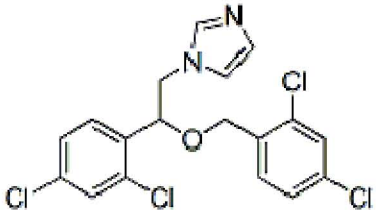
A review of the published literature regarding local tolerance of buccal adhesive preparations revealed that the most common adverse events reported with buccal tablets were gum or mouth irritation, bitter taste, gum pain, gum tenderness, gum edema, and taste perversion.

The literature search revealed that the most common effects reported with the ingestion of milk protein are allergic and allergenic responses. ORAVIG is contraindicated in patients with known hypersensitivity to milk protein concentrate.

2. DRUG INFORMATION

NDA number	22-404
Review number	1
Sequence number	9
Date of submission	June 16, 2009
Type of submission	Resubmission/After Refusal to file
Relevant INDs	69,578
Relevant NDA's	NDA 18-888, NDA 20968
Applicant	BioAlliance Pharma 59, Boulevard du General Martial Valin 75015 Paris France
Applicant's agent	Beckloff Associates Commerce Plaza II, Suite 300 7400 West 111th Street, Overland Park, KS 66210
Manufacturer for drug substance	(b) (4)
Manufacturer for drug product	
Reviewer name	Owen McMaster
Division name	Division of Special Pathogen and Transplant Products
HFD #	590
Review completion date	March 1, 2010
Drug class	Azole antifungal
Trade name	ORAVIG
Generic name	Miconazole
Chemical name	1-[2,4-Dichloro-®-[(2,4-dichlorobenzyl) oxy]phenethyl]-imidazole mononitrate.
Molecular formula	$C_{18}H_{14}Cl_4N_2O.HNO_3$
Molecular weight	479.15
Intended clinical population	Patients with oropharyngeal candidiasis

Miconazole



Clinical formulation:

ORAVIG is a buccal tablet that is attached to the upper gum just above the incisor tooth. As the tablet dissolves, miconazole is released into the saliva through which it is conveyed to the site of OPC infection. The composition of the tablet is shown below.

Table 2.3.P.1-1 Composition of Miconazole Lauriad® 50 mg MBT

Compound	Reference to Quality Standard	Function	Quantity per Tablet	
			mg	% w/w
Active Ingredient:				
Miconazole Base	Current USP	Drug Substance	50.00	43.48
Excipients:				(b) (4)
Hypromellose (b) (4)	Current USP			
Milk Protein Concentrate	In-house standard			
Maize Starch [b]	Current USP/NF			
Lactose Monohydrate	Current USP/NF			
Sodium Laurilsulfate [c]	Current USP/NF			
Magnesium Stearate	Current USP/NF			
Talc	Current USP			
				(b) (4)
		Total	115.00 [e]	100.00

(b) (4)

Route of administration: Buccal

3. STUDIES SUBMITTED

(1) Study 31370 TSH: Tolerance study after repeated topical application for two weeks on the jugal mucosa of hamster.
(2) Study 31466 TSH: Tolerance study after repeated topical application on the jugal mucosa of hamster: preliminary feasibility report.
(3) Study 31369 TSS: Evaluation of skin sensitization potential in mice using the local lymph node assay

10 SPECIAL TOXICOLOGY STUDIES

Local tolerance

Study title	Tolerance study after repeated topical application for two weeks on the jugal mucosa of hamster
Key study findings	Administration of ORAVIG ® (1000 mg/kg) into the cheek pouch of gold hamsters resulted in thinness, hypoactivity, sedation, stuck lips, closed/half closed eyes, reduced food and water consumption, reduced body weights and death. ORAVIG ® administration also resulted in hyperkeratosis, inflammation and dilated blood vessels in the mouth. The deaths clearly indicate that the doses tested were above the maximum tolerated dose.
Study no	31370 TSH
Conducting laboratory	(b) (4)
Date of study initiation	March 2, 2006
GLP compliance	No
QA report	Yes
Drug lot	E213X013
Formulation	Miconazole ORAVIG ® was ground to a fine powder then prepared as a paste with 0.9 % saline.

Purpose

This study was designed as a bridging study to evaluate the irritating potential of ORAVIG buccal tablets.

Methods

Species/strain: Gold hamsters *Mesocricetus auratus*
Number of test animals: 5/sex
Control group: 10 animals
Age: Animals were described as adult.
Weight: 76 to 78 g
Doses in administered units: 0.5 ml of ORAVIG ® paste

Route: Cheek pouch.
Dosing duration: Originally planned for 14 days, the study was stopped on Day 7.
Dose: About 1000 mg/kg

Observations and times:

Clinical signs: Daily
Mortality: Daily
Body weights: Day 1 and Day 4.
Food and water consumption: Days 1, 3 and 4.
Pathology: Day 7.

Results:

Mortality
No control animals died. Five of the ten drug-treated animals died between days 4 and 7.

Clinical signs

Clinical signs were recorded in the treated animals beginning on Day 4 included thinness, hypoactivity, sedation, stuck lips and closed/half closed eyes. Body weight losses were as high as 25 %; food consumption was reduced by as much as 62 % and water intake by as much as 83 %. Some of the test substance was rejected by all groups including controls. Residual test substance was detected in the cheek pouches of several animals. Dilated vessels were also noted in treated hamsters. On Day 6, the study was stopped because of the poor condition of the animals. All surviving animals were sacrificed and cheek pouches were examined microscopically.

Histopathology

The most prominent feature seen in test animals upon microscopic examination was increased thickness of the epithelium keratin layer, (hyperkeratosis) sometimes with inflammation and dilated blood vessels.

Summary

Administration of ORAVIG ® (1000 mg/kg) into the cheek pouch of gold hamsters resulted in thinness, hypoactivity, sedation, stuck lips, closed/half closed eyes, reduced food and water consumption, reduced body weights and death. ORAVIG ® administration also resulted in hyperkeratosis, inflammation and dilated blood vessels in the mouth. The deaths clearly indicate that the doses tested were above the maximum tolerated dose. The study was terminated early because of the deaths and the poor clinical condition of the animals.

Study title	Tolerance study after repeated topical application on the jugal mucosa of hamster: preliminary feasibility report.
Key study findings	Repeated administration of ORAVIG ® miconazole at 1000 mg/kg into the cheek pouch of hamsters causes deaths even if pouch is rinsed four hours after dosing.
Study no	31466 TSH
Conducting laboratory	(b) (4)
Date of study initiation	March 9, 2006
GLP compliance	No
QA report	Yes
Drug lot	E213X013
Formulation	Miconazole ORAVIG ® was ground to a fine powder then prepared as a paste with 0.9 % saline.

Purpose

This study represents the redesign of a bridging study to evaluate the irritating potential of ORAVIG buccal tablets. A similar, previous study of was terminated early because of the deaths and the poor clinical condition of the animals. These adverse effects were thought to be the result of rejection and swallowing of the test material. In the present study, the sponsor modified the experiment by rinsing the cheek pouch 4 hours after dosing, to reduce exposure to the drug product.

Methods

Dosing:
Species/strain: Gold hamsters *Mesocricetus auratus*
Number: 4
Control group: one male
Treated group: one male and two females
Age: Animals were described as adult.
Weight: 82 to 88 g
Doses in administered units: 0.5 ml of ORAVIG ® paste
Route: Cheek pouch. Cheek pouches were rinsed with saline 4 hours postdose to remove any residual drug product.
Times: Originally planned for 8 days, the study was stopped on Day 5.

Observations and times:
Clinical signs: Daily
Mortality: Daily
Body weights: Day 1 and Day 4.
Food and water consumption: Day 1 and Day 4.
Pathology: Day 5.

Results:

Mortality and clinical signs: The male hamster treated with miconazole was found dead on Day 5. Clinical signs observed prior to death included hypoactivity, sedation, recumbency, piloerection, dyspnea and tremors. The two females were hypoactive beginning on Day 4. The surviving animals were sacrificed on Day 5 due to poor condition. Body weights were reduced by around 20 % in treated animals. Food and water consumption were markedly decreased on days 3 and 4. Some visible blood vessels were observed upon macroscopic postmortem examination but there were no obvious changes to the major organs.

Summary

Administration of ORAVIG ® into the cheek pouch of gold hamsters with rinsing of the cheek pouch 4 hours post dose resulted in reduced food and water consumption, reduced body weights, hypoactivity, sedation, recumbency, piloerection, dyspnea, tremors and death. Some visible blood vessels were observed. The daily dose administered (1000 mg/kg) was clearly above the maximum tolerated dose and was over 5 times the known LD_{50} of miconazole in mice (160 mg/kg). Due to adverse events which the study director attributed to systemic toxicity, the planned 8-day treatment could not be completed, even though pouches were rinsed four hours after administration of drug.

Study title	Evaluation of skin sensitization potential in mice using the local lymph node assay
Key study findings	No contact hypersensitivity was detected
Study no	31369 TSS
Conducting laboratory	(b) (4)
Date of study initiation	March 2, 2006
GLP compliance	Yes
QA report	Yes
Drug lot	E213X013
Formulation	Miconazole ORAVIG ® was ground to a fine powder then prepared at the chosen concentrations in propylene glycol

Purpose

This study was conducted to evaluate the potential of ORAVIG to induce delayed contact hypersensitivity using the murine Local Lymph Node Assay.

Methods

Species/strain	Female CBA/J mice
Number/group	4
Age	9 weeks
Weight	21 g
Doses	0.25, 0.5, 1, 2.5 or 5 %
Route	Topical
Volume	25 µl over each ear
Frequency	Once daily on days 1-3

Proliferation Assay:
On day 6 all animals received a single intravenous injection of 0.9 % NaCl containing 20 µCi of ^{3}H-thymidine (^{3}H-TdR) via the tail vein. Five hours later they were sacrificed and the auricular lymph nodes excised and proliferation determined. Positive control animals were treated with 25 % HCA (α-hexylcinnamaldehyde)

Observations and times:
Clinical signs: Daily
Body weights: Days 1 and 6
Ear thickness: Days 1, 2, 3 and 6.
Irritation: Days 1, 2, 3 and 6.
Results:

Mortality: No mortality was observed
Clinical signs: No clinical signs were observed
Body weights: No changes in body weight were observed

Table 1. Irritation and Stimulation Index in mice treated with ORAVIG

Treatment	Irritation Level	Stimulation Index
ORAVIG 0.5 %	Non-irritant	0.69
ORAVIG 1 %	Non-irritant	1.02
ORAVIG 2.5 %	Non-irritant	0.79
ORAVIG 5 %	Non-irritant	1.08
ORAVIG 0.25 %	Non-irritant	1.7
HCA 25 %	Positive Control	14.84

SI was calculated from the following formula:

$$SI = \frac{\text{dpm of treated group}}{\text{dpm of control group}}$$

Interpretation of results: An agent was considered a skin sensitizer when the SI for the group was greater than or equal to 3.

Summary

No local irritation was recorded at concentrations up to 5 % miconazole and no significant lymphoproliferation based on the Stimulation Index was recorded in any ORAVIG-treated mice.

Milk protein concentrate (MPC)

The applicant included a summary of findings from a literature review on milk protein concentrate (MPC), a component of ORAVIG buccal tablet. The following is excerpted from the applicant's discussion.

(b) (4)

The MPC was produced in New Zealand by the New Zealand manufacturer (b) (4) and was considered unlikely to present any transmissible spongiform encephalopathy risk. They were considered compliant with Chapter 6.6: *Milk and Milk Derivatives of the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products* ([European Guideline EMEA/410/01 Rev. 2— October 2003] adopted by the Committee for Proprietary Medicinal Products [CPMP] and by the Committee for Veterinary Medicinal Products [CVMP]) and with the *Note for guidance for minimizing the risk of transmitting agents causing spongiform encephalopathy via veterinary medicinal products* (European Union BSE Note for Guidance. III/3385/92-EN; January 27, 1993) since (1) The milk was sourced from healthy animals under the same conditions as milk collected for human consumption; and (2) No other ruminant materials, with the exception of calf rennet, are used in the preparation of such derivatives.

The applicant also cited a Center for Food Safety and Applied Nutrition (CFSAN/FDA) which concluded that "BSE is not transmitted in cow's milk even if the milk comes from a cow with BSE and that Milk and milk products, even in countries with high incidence of BSE are, therefore, considered safe." BSE (FDA/CFSAN Report, January 14, 2004; Updated July 9, 2004, Commonly Asked Question about BSE in products regulated by FDA's Center for Food Safety and Applied Nutrition (CFSAN)).

The most common effects reported with the ingestion of milk protein are allergic and allergenic responses. Cow's milk contains more than 25 proteins capable of inducing a specific antibody response in humans. Of these, the most allergenic component is β-lactoglobulin, followed by casein. Allergy to the components of cow's milk occurs most often in infants and young children with an estimated prevalence of 0.5% to 7.5%. While allergy to the components of cow's milk can persist into adulthood, these typically diminish with advancing age with a prevalence of 0.1% to 0.5% in adults. In animal studies of milk proteins, heating at 90 degrees C and ultrafiltration to remove all peptides with high molecular weights (< 2500 Da) eliminated the sensitizing capacity of some, but not all milk proteins.

ORAVIG buccal tablets contain (b) (4) of MPC and potential allergic reaction cannot be excluded. The product's labeling will clearly state that it contains milk protein and that the product should not be used in patients with known hypersensitivity to milk protein concentrate

11 INTEGRATED SUMMARY AND SAFETY EVALUATION

The applicant has submitted a 505(b) (2) application requesting marketing approval for ORAVIG, a buccal tablet containing 50 mg of miconazole, which is to be applied to the upper gum region (canine fossa) once daily for 14 consecutive days.

Miconazole is an imidazole antifungal that has been approved for use in many countries for over three decades, but it is only approved as intravaginal and dermal formulations in the US. An oral formulation (Daktarin® oral gel) is available in other countries.

The approved miconazole dose of the oral gel is around 250 mg/day but clinical trials in North African patients have studied doses of 500 mg/day for 14 days. Given extensive clinical experience with higher oral doses of miconazole, the proposed dose of miconazole in ORAVIG, 50 mg/day, appears to be safe. BioAlliance Pharma therefore conducted a limited toxicology program with ORAVIG to evaluate the potential of this new formulation to cause irritation and to induce delayed contact hypersensitivity.

Two bridging nonclinical toxicology studies were conducted to evaluate the irritating potential of ORAVIG. Tablets were finely crushed and prepared into a paste with 0.9 % saline, which was then administered into the cheek pouch of gold hamsters (*Mesocricetus auratus)*. In the first study, adverse effects, beginning on Day 4, included hypoactivity, sedation, recumbency, piloerection, dyspnea, tremors and death, and both control and test animals rejected material from the cheek pouch. The study was therefore stopped on Day 5. An attempt to repeat the experiment with reduced exposure times (the cheek pouch was rinsed after 4 hours) was also unsuccessful due to ORAVIG rejection and adverse effects (markedly decreased food and water consumption, marked body weight losses, poor clinical conditions in all animals and mortality in 1/3 animals on day 5). The adverse effects were likely due to rejection of material, swallowing and systemic exposure to the drug, as the dose (1000 mg/kg/day) was above the acute LD_{50} values known for other species (160-276 mg/kg). The jugal mucosa of surviving animals showed orthokeratotic hyperkeratosis which was sometimes associated with minimal inflammation and dilated blood vessels. The hamster cheek pouch model was therefore not useful in evaluating the irritation potential of ORAVIG over 14 days, since the adverse events precluded continued exposure of the oral mucosa beyond Day 5.

The results of these studies are not totally unexpected as retention of the test material is often poor in the hamster cheek pouch model. Some investigators have even tried securing the test substance by means of suturing but the hamsters would often turn the pouches inside-out and chew through the sutures. Also, the tissue injury caused by the sutures confounded the interpretation of any histopathological findings that were detected. One ‘pouch-in-pouch’ technique claims to have improved the model and achieved a retention rate of 97-100% at the end of 14 days [Harsanyi, B.B., Foong, W.C., Howell, R.E., Hidi, P. and Jones, D.W. (1991): Hamster Cheek-pouch Testing of Dental Soft Polymers. J Dent Res 70(6):991-996].

At this point in the development of ORAVIG, additional nonclinical toxicology studies will not provide any data that will improve the safe use of this drug since:

(1) The safety of this 50 mg/kg dose of miconazole by the oral route has been established by clinical data, including data at much higher doses.
(2) The risk that patients with milk protein intolerance could experience adverse reactions from ORAVIG has been addressed since the drug has been contraindicated in persons with known hypersensitivity to milk protein concentrate.
(3) The applicant has twice attempted to evaluate the irritation potential of ORAVIG in hamsters without success. While the "pouch-in-pouch" technique may increase retention of the test material, this could require repeated suturing of the hamster cheek pouch, which could confound interpretation of any findings.
(4) Based on the limited nonclinical data obtained in the hamster cheek pouch studies, the irritant effects of ORAVIG appear to be mild. After 5 days, the jugal mucosa of surviving animals revealed orthokeratotic hyperkeratosis which was sometimes associated with minimal inflammation and dilated blood vessels. The medical officer has concluded that local adverse events reported in clinical trials of ORAVIG were similar to local adverse events reported for miconazole gel and for clotrimazole troche (see Clinical Review by Medical Officer Dr. Hala Shamsuddin).
(5) ORAVIG did not induce contact hypersensitivity in mice in the local lymph node assay. ORAVIG did not cause significant lymphoproliferation or local irritation at concentrations up to 5 %.

The applicant had proposed to include data from NDA 20-968 (labeling and a redacted, publicly available Pharmacology/Toxicology review) in the prescribing information, but this was not allowed because NDA 20-968 is no longer listed in the Orange Book. The information in the label instead came from the results of original studies submitted with this NDA, publicly available prescribing information (from MONISTAT® 3 and Monistat IV labeling), and the following journal articles:

Sawyer, P.R., Brogden, R.N., Pinder, R.M., Speight, T.M., and Avery, G.S. 1975. Miconazole: a review of its antifungal activity and therapeutic efficacy. *Drugs*. 9(6):406-23.

Hassan, N. and Hassan, A. 1997. Miconazole Genotoxicity in Mice. *J. Appl. Toxicol*., 17(5) 313–319.

Vanparys, P., Vermeiren, F., Sysmans, M. and Temmerman, R. 1990. The micronucleus assay as a test for the detection of aneugenic activity. *Mutation Research Letters*, 244 (2): 95-103.

Tiboni, G.M., Marotta, F. and Castigliego A.P. 2008. Teratogenic effects in mouse fetuses subjected to the concurrent in utero exposure to miconazole and metronidazole. Reprod Toxicol. 26 (3-4):254-61.

Voogd, C.E. and van der Stel, J.J. 1983. Are econazole, miconazole and clotrimazole mutagenic to bacteria? Mutation Research Letters. 120, (2-3): 91-95.

Please see the **SUGGESTED LABELING** section, below for proposed wording based on these data.

In summary, ORAVIG has been studied in clinical and nonclinical studies and besides being contraindicated in patients with known hypersensitivity to its components, there are no toxicological concerns. No additional nonclinical studies are being recommended at this time.

SUGGESTED LABELING:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled clinical trials of ORAVIG in pregnant women. ORAVIG should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

Miconazole nitrate administered orally at doses of 80 mg/kg/day or higher to pregnant rats or rabbits crossed the placenta and resulted in embryo- and fetotoxicity, including increased fetal resorptions. These doses also resulted in prolonged gestation and dystocia in rats, but not in rabbits. Embryofetotoxicity was not observed in intravenous studies with miconazole at lower doses of 40 mg/kg/day in rats and 20 mg/kg/day in rabbits, which are approximately 8 times higher than the dose a patient would receive if she swallowed an ORAVIG buccal tablet, based on body surface area comparisons. Teratogenicity was not reported in any animal study with miconazole.

8.3 Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ORAVIG is administered to a nursing woman.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with miconazole have not been conducted.

Miconazole nitrate was not genotoxic when tested *in vitro* in a bacterial reverse mutation (Ames) assay or in an *in vivo* mouse bone marrow micronucleus test. Intraperitoneal injections of miconazole to mice induced chromosomal aberrations in spermatocytes and bone marrow cells, and morphologic abnormalities in sperm at doses similar to or below clinical doses. However, no impairment of fertility was observed in intravenous studies with miconazole at 40 mg/kg/day in rats or 20 mg/kg/day in rabbits, which are approximately 8 times higher than the dose a patient would receive if she swallowed an ORAVIG buccal tablet, based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

Local tolerance studies (LLNA sensitization test and tolerance study on the jugal mucosa of hamster) did not reveal any toxicity.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole (b) (4) (b) (4) tablet)

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/s/

OWEN G MCMASTER
04/14/2010

WILLIAM H Taylor
04/15/2010
See also Pharmacology/Toxicology Supervisor's review.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22-404 **Applicant:** BioAlliance Pharma **Stamp Date: June 16, 2009**

Drug Name: Lauriad (miconazole (b) (4) buccal tablet) **NDA Type:**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		Proposed limits may have to be adjusted.
11	Has the applicant addressed any abuse potential issues in the submission?			**Not Applicable**
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			**Not Applicable**

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

OWEN G MCMASTER
08/19/2009

WILLIAM H Taylor
08/19/2009

PHARMACOLOGY/TOXICOLOGY NDA FILING CHECKLIST

NDA Number: 22-404 **Applicant:** BioAlliancePharma **Stamp Date:** February 6, 2009

Drug Name: Lauriad (miconazole) (b) (4) Buccal Tablet **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		
8	Has the applicant submitted all special Studies or data requested by the Division during pre-submission discussions?	√		

PHARMACOLOGY/TOXICOLOGY NDA FILING CHECKLIST

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		New limits may have to be proposed.
11	Has the applicant addressed any abuse potential issues in the submission?			**Not Applicable**
12	If this NDA/BLA is to support an Rx to OTC switch, have all relevant studies been submitted?			**Not Applicable**

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

Owen McMaster
4/10/2009 02:55:30 PM
PHARMACOLOGIST

William Taylor
4/10/2009 03:00:14 PM
PHARMACOLOGIST